

**SUPPORT AND MANAGEMENT FOR THE PROJECT:
 "EFFECTS OF THE CHORNOBYL ACCIDENT ON THYROID CANCER AND LEUKEMIA"
 CONTRACT BETWEEN NATIONAL CANCER INSTITUTE AND THE TRUSTEES OF
 COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
 QUARTERLY PROGRESS REPORT, SEPTEMBER 30 - DECEMBER 31, 2000**

1. Introduction

This report covers activities carried out during the first quarter of the fourth year of the contract between the National Cancer Institute (NCI) and Columbia University for the support of thyroid cancer studies in children in Belarus and Ukraine and leukemia in clean-up workers in Ukraine. Trips by Columbia investigators and consultants made in connection with the studies are summarized in Section 2. Other relevant scientific activities are detailed in Sections 3 and 4. Administrative activities are detailed in Section 5 and an outline of projected activities for the second quarter of the fourth year is given in Section 6.

2. Trips by Columbia Investigators and Consultants (September 30 to December 31, 2000)

These trips are summarized in the table below. Trip reports have been submitted to NCI and brief summaries of these reports are included in Section 2.1.

Name	Place	Purpose	Date
Howe	Kiev	Thyroid, leukemia	Sept. 25-30, 2000
Howe	NCI	COP	Oct. 2, 2000
Howe	Lyon	Leukemia	Oct. 16-18, 2000
Finch	Kiev	Leukemia	Oct. 16-20, 2000
Hodgson	Kiev	Thyroid	Oct. 17, 18, 20, 2000
Hodgson	Kiev	Leukemia	Oct. 19, 2000
Howe	Kiev	Leukemia	Oct. 19-20, 2000
Hodgson	Minsk	Thyroid	Oct. 23-25, 2000
Howe, Brill, Fink, Greenebaum, McConnell, Robbins, Burch, Hodgson	NCI	Tri-National meeting	Nov. 13-17, 2000
Howe	Kiev	Thyroid, leukemia	Dec. 4-8, 2000

Name	Place	Purpose	Date
Greenebaum	Kiev	Thyroid	Dec. 7-8, 2000
Fink	Kiev	Thyroid	Dec. 7-8, 2000
McConnell	Kiev	Thyroid	Dec. 7-8, 2000
Robbins	Kiev	Thyroid	Dec. 7-8, 2000
Greenebaum	Minsk	Thyroid	Dec. 11-13, 2000
Fink	Minsk	Thyroid	Dec. 11-13, 2000
McConnell	Minsk	Thyroid	Dec. 11-13, 2000
Robbins	Minsk	Thyroid	Dec. 11-13, 2000
Howe	NCI	COP	Dec. 11, 2000

2.1 Summaries of Trip Reports:

Dr. G R. Howe, Kiev, Leukemia and Thyroid Studies (September 25-30, 2000):

A number of issues were discussed with regard to the leukemia study including the preparation for and participation in the training workshop for oblast staff taking part in the leukemia study. Also future directions for leukemia dosimetry were discussed.

With respect to the thyroid study. Dr. Howe participated in the joint thyroid dosimetry meeting between Belarusians, Ukrainians and U.S. scientists to revise the new dosimetry questionnaire to be used for second screening. In addition Dr. Howe met with the Kiev thyroid personnel to discuss a number of issues including pre-testing the dosimetry questionnaire, a full training session (to take place in Kiev in February of 2001), for second round screening, streamlining supplies to Ukraine, and the purchase of computers for the Epidemiology group.

Dr. G. R. Howe, Lyon, Leukemia, October 16-18, 2000:

The purpose of the visit to Lyon was to attend the meeting of the Joint Dosimetry Epidemiology Group working on the leukemia study. The meeting focused on further development of the modified analytic dose reconstruction technique and in particular, systematizing procedures and making them

more uniform. An important part of this will be to construct in final form a data base of exposure rate measurements which can be used in conjunction with questionnaire data to provide reproducible doses. It was agreed that Dr. Chumak would initiate a fuller comparison study of MADR and EPR in which 50 individuals with teeth containing adequate buccal and lingual material and with no evidence of dental x-rays would be interviewed to form a basis for an appropriate comparison. A number of possible techniques for handling measurement error were also discussed and it seemed likely that the effect of measurement error, as it impacts upon risk estimation, may have to be handled by Monte Carlo simulation.

Dr. S. Finch, Kiev, Leukemia, October 16-20, 2000:

Discussions were held with the hematologists and epidemiologists regarding revised plans and current progress for the identification of cases with leukemia, myelodysplasia and multiple myeloma in Kiev City and the five oblasts in the study. Major discussion focused on completeness of ascertainment in each of the study areas. In addition, issues such as schedules for completion of tasks during the next two years, content of hematology information for the operations manual, various ways of recording clinical and laboratory information for case confirmation, criteria for the diagnosis of multiple myeloma, and plans for creation of a hematology repository at the RCRM were discussed. In a separate meeting with the hematologists detailed plans for the collection and processing of buccal cells were discussed.

An in-depth review of the medical system and various mechanisms for the identification of cases of leukemia, myelodysplasia and multiple myeloma in the Chernikiv oblast was done at the Public Health Office and Oncology Hospital in Chernikiv.

S. Hodgson, Kiev, Thyroid, October 17, 18, 20, 2000:

Ms. Hodgson reviewed the various laboratories and other study sites to ensure that she had the necessary information for inventory. An inventory was completed for each department in the study

and bar coded. The issue of supplies was also discussed with emphasis placed on the necessary documentation needed to clear Customs in Ukraine.

S. Hodgson, Kiev, Leukemia, October 19, 2000:

An inventory for the leukemia study was completed for 69 pieces of equipment and bar coded. Problems with Customs clearance were discussed.

Dr. G R. Howe, Kiev, Leukemia, October 19-20, 2000:

Progress in assembling the leukemia registry was discussed. This appears to be well on course and a priority item now is to set up a suitable data base system when the computers have been purchased. It was suggested that for the time being this can be started on existing equipment. It was also agreed that by the next visit in December the new data manager (Yuri Byelyaev) would have designed an appropriate data entry system and editing programs.

S. Hodgson, Minsk, Thyroid, October 23-25, 2000:

Year 2001 supplies were discussed and an inventory of equipment was completed and bar coded. Purchasing of requested items for 2000 were listed with items ordered and not received identified together with items not yet ordered. These latter two items will receive top priority.

Dr. G. R. Howe, Kiev, Thyroid, December 4-8, 2000:

Dr. Howe met with Dr. Thomas and Dr. Tronko and staff from both Belarus and Ukraine to outline the necessary preparations for re-screening and re-training, with the latter to take place in Kiev and Minsk in February, 2001. This included revisions to the Operations Manual and screening forms. In this respect a foundation was laid for reformatting the endocrine summary form in order to come up with a common form.

In addition, Dr. Howe worked with Dr. Thomas in a two-day training session of two interviewers from each of Belarus and Ukraine who will be pre-testing the new dosimetry questionnaire.

With regard to the leukemia study progress to date in establishing the data base for the leukemia registry was reviewed and expert advice was given on the day to day routine edit checks necessary to be implemented in data processing. Additionally, project supervisors from Kiev City and Kiev oblast presented an overview of data sources available to aid in the creation of the leukemia registry.

Dr. E. Greenebaum, Kiev, Thyroid, December 7-8, 2000:

Dr. Greenebaum was given the opportunity for a final review of cytology forms and an intensive slide review. She reviewed Fine Needle Aspiration biopsies from 34 cohort members and 208 slides. Overall, she agreed with most of the diagnoses and did not find any missed cases of cancer. The proportion of cases classified as "diagnostic reliability is limited by limited cellularity" or "non-diagnostic due to insufficient cellularity" was found to be acceptable. She found that any differences of opinion regarding specimen adequacy assessment were minor and had been noted on the forms as "expert opinion". At the time of her visit Dr. Greenebaum made some recommendations on changing the cytology forms and these were provided to Dr. Terry Thomas in order to prepare the final cytology form.

Dr. D. Fink, Kiev, Thyroid, December 7-8, 2000:

Dr. Fink reported that the supply situation is much improved compared to previous visits with general satisfaction with the state of inventories and that the testing is proceeding in a satisfactory fashion although quality control practices still require some improvement. Nonetheless, a comparison of the quality control results from Kiev and Minsk show excellent agreement. Results of the normal range were available for analysis and are being written up separately.

With respect to thyroglobulin (TG) testing all that was hoped for was not accomplished during the trip because of time constraints but there seemed to be a relationship between TG levels and diagnostic groups but not thyroid volume, TSH or urinary iodine. This is at variance from data which was later received from Minsk which suggests relationships to size, volume, iodine and TSH. Dr. Fink suggests that the Ukrainian data be tabulated in a fashion similar to the data from Minsk and

then a comparison made. At this point in time, Dr. Fink recommends that TG testing be continued for the second screening cycle in order to accumulate more data on TG levels based on an increasing number of abnormal diagnoses.

Dr. R. McConnell, Kiev, Thyroid, December 7-8, 2000:

Dr. McConnell, along with other members of the clinical working team, reviewed records of patients with thyroid nodules and cancer, examined thyroglobulin data by clinical diagnosis and discussed with the relevant staff re-training prior to second screening. A major accomplishment of the trip was the establishment of criteria for the diagnosis of auto immune thyroiditis.

Dr. J. Robbins, Kiev, Thyroid, December 7-8, 2000:

Dr. Robbins met with members of the clinical team and their counterparts in Kiev to review case records and to discuss matters related to clinical diagnosis, clinical referrals, and retraining and other preparations for the second screening cycle. Twenty records were reviewed and discussed, comprising patients with newly discovered thyroid nodules and thyroid cancer.

Dr. E. Greenebaum, Minsk, Thyroid, December 11- 13, 2000:

Dr. Greenebaum was provided the opportunity for a final review of cytology forms and an intensive slide review. In this respect she reviewed 18 FNA biopsies and 96 slides, resolving some of the disputed diagnoses of clinically challenging cases. In addition she noted that the inadequacy rate has declined and hopes that is a trend. She reports that the Diff Quick stain is finally being used but that there are some problems with instructions which were resolved and will be re-evaluated on her next trip. On her first trip to Aksakovchina she reviewed the ultrasound and cytology facilities and met key personnel, detected some protocol problems, demonstrated smear preparation techniques and identified the need for some basic supplies.

Dr. D. Fink, Minsk, Thyroid, December 11-13, 2000:

Dr. Fink reports that the supply situation is much improved compared to previous visits and there is general satisfaction with the state of inventories. The testing is proceeding in a satisfactory fashion and a comparison of the quality control results from Minsk and Kiev show excellent agreement. However, a normal range study must be performed on the most suitable population even if it is not ideal.

With respect to thyroglobulin (TG) testing, all that was hoped to be accomplished was not, due to a break in at the DCC. Data provided by Dr. Polyanskaya after the visit suggests that relationships do exist between thyroid volume, urinary iodine, and TG. At this point Dr. Fink recommends that TG testing be continued for the second screening cycle in order to accumulate more data on TG levels based on an increasing number of abnormal diagnoses.

Dr. R. McConnell, Minsk, Thyroid, December 11-13, 2000:

Together with other members of the clinical team Dr. McConnell reviewed records of patients with thyroid nodules and cancer, examined thyroglobulin data by clinical diagnosis and discussed with relevant staff retraining in February 2001 prior to second screening. A major accomplishment of the trip was establishment of criteria for auto immune thyroiditis diagnosis.

Dr. J. Robbins, Minsk, Thyroid, December 11- 3, 2000:

Dr. Robbins reviewed case records and discussed matters related to clinical diagnosis, clinical referrals and retraining and other preparations for the second screening cycle. Thirty seven records of newly discovered thyroid nodules and thyroid cancers were reviewed and discussed.

3. Thyroid Study

During the course of the present quarter much work has concentrated on preparation for second screening which is scheduled to begin in 2001 in both Belarus and Ukraine. In this respect Dr. Howe and Professor Burch worked closely with Dr. Thomas on the revision of screening forms in order

that the forms for second screening in Belarus and Ukraine be as similar as possible. Time was also spent in revising the dosimetry questionnaire, preparations for gearing up for second screening and the proposed training program in Kiev (February 7-9, 2000) and in Minsk (February 12-14) (see Section 6.2 below).

Drs. McConnell and Robbins (members of the Columbia clinical team) assisted the Belarusian and Ukrainian colleagues with composing poster presentations for the 12th International Thyroid Congress, which was held in Kyoto, Japan on October 22-27, 2000. The Belarusian abstract concerned the prevalence of thyroid auto antibodies in the cohort, while the Ukrainian contribution concentrated on the prevalence of thyroid nodules and cancer.

Members of the Columbia team also prepared for and attended the Tri-National meeting in Rockville, Maryland, November 13-15, 2000, which included re-training procedures, publication policy, joint clinical forms and changes to the Operations Manuals and a thorough review of screening issues. Topics discussed at the clinical breakout sessions included criteria for auto immune thyroiditis (AIT), referral to surgery, FNA biopsy, FNA performed by the mobile teams, follow-up of missed FNA and surgery, routine assays for thyroglobulin and anti-thyroglobulin antibodies, management of the non operated thyroid nodule, classification of nodules smaller than 5mm, and post operative management of patients with benign disease. Agreement was reached on criteria for FNA and partial accord achieved on referral to surgery.

Work has also been accomplished on drafting outlines of one or two papers describing study design and power, and study results (except those which are dose related). This is being done in collaboration with other U.S. investigators and Belarusian and Ukrainian investigators and will continue into the next quarter.

4. Leukemia Study

Dr. Howe, in collaboration with other U.S. investigators and scientists from Ukraine, has continued to oversee the assembly of the leukemia registry and the establishment of a suitable data base including day-to-day routine edit checks and quality control.

Dr. Finch, together with Professor Burch, colleagues in Ukraine (Drs. Dyagil, Gudzenko, and Klimenko) and other scientists in the U.S., has written a paper for publication in the peer reviewed literature on a review (the week of January 9, 1999) in Kiev of slides and abstracted medical records from cases of randomly selected males in the general population of specific regions of Ukraine. The review consisted of a group of highly qualified hematologists from France, the Ukraine and the U.S. and its primary objective was to determine the extent to which the diagnosis and classification of leukemia might be histologically verified by western standards in Chernobyl accident clean up workers. The results of the study strongly suggest that hematologists in Ukraine and other western countries agree well on the diagnosis and classification of acute and chronic forms of leukemia. (See Appendix One for the title page and abstract of this paper)

5. Administrative Activities:

Administrative activities in the first quarter of Option Year One centered on reporting of the work efforts of Years 1-3. The annual report was completed and the purchasing report updated to include all purchases made on behalf of NCI. A separate listing of each item requested and its order status (ordered and shipped, order pending, not yet ordered) was prepared and S. Hodgson reviewed these lists during her trips to Kiev and Minsk. She met with appropriate personnel at all three study sites to compare her prepared lists with actual deliveries received and to reach agreement on orders yet to be received. Upon her return to Columbia final purchasing actions to complete all of the approved requests to date were initiated. A copy of the final listing of supplies and equipment ordered by Columbia was sent to NCI for their review.

In meetings with Dr. Howe, Ms. Hodgson, Mr. Illian and Dr. Zablotska, a purchasing database was outlined to provide ongoing reporting capability. Dr. Zablotska is designing this database and we believe that it will enable us to provide Dr. Masnyk and Ms. Stein with the current status of approved purchasing requests.

Payment was made to the Research Clinical Institute of Radiation and Endocrinology in Minsk in the amount of \$89,318.00. At the Tri-National Meetings in November we were informed that the Belarus Government taxed this money at the rate of 60%. Drs. Masnyk and Howe as well Ms. Hodgson and Miller are working to investigate possible alternative methods of payment.

In response to the departure of Dr. Kokoreva, changes were made in the processing the travel reimbursements. Dr. Zablotska took over these responsibilities and developed a database in MS Access to monitor receipt of reimbursement requests and issuance of checks.

Mr. Illian assumed the responsibility of a central filing system. He moved files from Dr. Kokoreva's office to a central location and has worked to re-organize the files to a more accessible system. Mr. Illian also worked with Ms. Hodgson to increase his ability to act in Ms. Hodgson's absence so that the office will be able to continue smooth operations.

Plans for the next quarter focus on purchasing of the next year's requests from Belarus when they are approved by Dr. Masnyk and providing support for the training sessions planned in both Kiev and Minsk.

Columbia University has been given the task of ensuring that all Columbia investigators and consultants have received appropriate training in human subjects issues and providing such training for our colleagues in Belarus and Ukraine.

All Columbia investigators and consultants have been requested to complete the appropriate training which each of their respective institutions provides and to also provide certification of having passed examinations in this training.

With regard to the Belarusians and Ukrainians a one day course based on the course taught at Columbia is being planned for both Kiev and Minsk in February (see Section 6.2) . It is anticipated that the course will be taught by Dr. Richard Sohn, Director of the Office of Grants and Contracts at Columbia University, who is responsible for the Columbia University course. The course will be translated into Russian and care taken not to offend the sensibilities of our colleagues in Belarus and Ukraine who have had many years of conducting studies amongst human subjects.

6. Proposed Activities for Next Quarter (January 1-March 31, 2001):

6.1 Timetable:

Name	Place	Purpose	Date
Howe	Kiev	Leukemia	Feb. 5-6, 2001
Finch	Kiev	Leukemia	Feb. 5-9, 2001
Brill, Burch, Fink, Howe, McConnell, Robbins, Zablotska	Kiev	Thyroid	Feb. 7-9, 2001
Sohn	Kiev	Thyroid, leukemia	Feb. 9, 2001
Sohn	Minsk	Thyroid	Feb. 12, 2001
Brill, Burch, Fink, Greenebaum, Howe, McConnell, Robbins, Zablotska	Minsk	Thyroid	Feb. 12-14, 2001
Howe	Minsk	Thyroid dosimetry	March 14-16, 2001
Howe	Kiev	Bi-National meeting	March 27-30, 2001

6.2 Training Sessions for Study Personnel Prior to Initiation of Second Screening in the Thyroid Studies:

It is planned to have a full training session for all those study personnel in both Belarus and Ukraine who will be administering the revised dosimetry questionnaire to cohort members together with personnel involved in laboratory procedures, screening endocrinologists, and study oblast staff in both Ukraine and Belarus. The Ukrainian sessions will be in Kiev, February 7-9 and the Belarusian sessions will be in Minsk, February 12-14. (See Appendix 2 for a description of the proposed training sessions in Kiev and Minsk.)

6.3 Leukemia Study: During the next quarter several major tasks and their fulfillment will have to be assessed including the ongoing establishment of the leukemia registry, installation of the data management system, monitoring that system and preparation of software for record linkage of the cohort to the leukemia registry. Hematological tasks include reevaluating the role of pathology in case identification and verification and finalizing hematology instructions for the Operations Manual.

APPENDIX 1

Title Page and Abstract of Paper on International Hematology Review

Title:

Histologic Verification of Leukemia, Myelodysplasia and Multiple Melanoma in Males in Ukraine, Ages 20-60, 1987-1998.

Dyagil I (1), Gudzenko N (1), Klimenko V (1), Burch J.D. (2) and Finch S C (3)

1. Research Center for Radiation Medicine, Kiev, Ukraine
2. Columbia University, New York, New York, USA
3. University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Camden, New Jersey, USA

Abstract

In preparation for a possible large epidemiological study of radiation related leukemia in Chornobyl clean up workers of Ukraine histological evaluation of 62 cases of leukemia and related disorders was conducted by a panel of expert hematologists from the United States, France and Ukraine. All cases were randomly selected from a population of males in the general population of six regions of Ukraine who were between the ages of 20 and 60 years at the time of the Chornobyl accident and had developed leukemia, myelodysplasia or multiple myeloma between the years of 1987 and 1998. The results of the study strongly suggest hematologists in Ukraine and other western countries agree well on the diagnosis and classification of acute and chronic forms of leukemia.

APPENDIX 2

Proposed Training Program, Kiev, February 7-9, 2001

The training for interviewers for the new dosimetry questionnaire will be done by Drs. Howe and Thomas and Ukrainian scientists. Dr. Fink and Ukrainian scientists will participate in training in laboratory procedures while Drs. McConnell and Robbins together with Ukrainian scientists will focus on training in endocrinology. Dr. Richard Sohn from Columbia University will lead a session on human subjects.

The proposed program follows:

1. Training for interviewers: All personnel who will be involved in administering the new dosimetry questionnaire to cohort members will be trained using the interviewer's manual. Practice interviews will be used as a basic training method.

2. Laboratory procedures: All personnel involved in laboratory procedures will be trained with an emphasis on the following:

- a) review of the operations manual
- b) review of phlebotomy techniques and re-certification requirements
- c) review of specimen processing techniques including duration of centrifugation, aliquoting and storage requirements
- d) blood borne pathogens

3. Endocrinology: Training involving endocrinology will be aimed at screening endocrinologists both from the fixed center and the mobile teams. Attention will be focused on:

- a) a review of changes to the Operations Manual
- b) changes to the clinical forms

- c) instructions for filling out the clinical forms
- d) a review of frequent mistakes made while filling out the forms
- e) discussion of referral procedures and problems and follow up for abnormalities detected during screening.

4. Human subjects: This training session will be aimed at all Ukrainian scientists and other personnel who have direct involvement with cohort members in both the thyroid and leukemia studies with an emphasis on dealing with human subjects in the study (e.g., confidentiality). Opportunities will be provided for questions and discussion.

Proposed Training Program, Minsk, February 12-14, 2001

Drs. Howe and Thomas, together with Belarusian scientists, will be involved with training of interviewers for the new dosimetry questionnaire. Dr. Fink together with Belarusian scientists will focus on training in laboratory procedures and Drs. McConnell and Robbins with Belarusian scientists will focus on training in Endocrinology. Dr. E. Greenebaum and Belarussian scientists will engage in training on cytology. Dr. Richard Sohn from Columbia University will lead a session on human subjects.

The proposed program follows:

- 1. Briefing of Belarusian scientific staff on progress to date and plans for second screening.**
- 2. Human subjects:** This training session will be aimed at all Belarusian scientists and other personnel who have direct involvement with cohort members with an emphasis on dealing with human subjects in the study (e.g., confidentiality). Opportunities will be provided for questions and discussion.
- 3. Training for interviewers:** All personnel who will be involved in administering the new dosimetry questionnaire to cohort members will be trained using the interviewer's manual. Practice

interviews will be used as a basic training method.

4. Laboratory procedures: All personnel involved in laboratory procedures including those from Gomel will be trained with an emphasis on the following:

- a) review of the Operations Manual
- b) review of phlebotomy techniques and re-certification requirements
- c) review of specimen processing techniques including duration of centrifugation, aliquoting and storage procedures
- d) blood borne pathogens.

5. Endocrinology: Training will be aimed at the screening endocrinologists both from the fixed centers (Minsk and Gomel) and the mobile teams. Attention will be focused on:

- a) a review of changes to the Operations Manual
- b) changes to the clinical forms
- c) instructions for filling out the clinical forms
- d) a review of frequent mistakes made while filling out the forms
- e) discussion of referral procedures and problems and follow up for abnormalities detected during screening.

6. Cytology: Two separate training sessions are planned. The first one will involve all cytologists from Gomel, Aksakovchina, the Oncopathology Center and the Dispensary and will focus on diagnostic criteria and form completion. The second session will involve all sonographers from Gomel, Assakovchina, the Oncopathology Center and the Dispensary and will focus on reviewing both aspiration and slide preparation techniques.